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DOCKET NO.: CP 380F
Application No.: 10/776,504
Office Action Dated: January 24, 2007

PATENT
REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

REMARKS

Following entry of the foregoing amendments, claims 1, 3 to 11, 19 to 22, and 24 will be pending in the application. Claim 1 has been amended and claim 12 has been canceled, herein, without prejudice. No new claims have been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

A. Claims 1, 3 to 12, 19 to 22, and 24 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Shen, *et al.*, *Blood*, 1997, 89(9), 3354-3360 ("the Shen article") in view of Chen, *et al.*, *Blood*, 1997, 89(9), 3345-3353 ("the Chen article"), Kwong, *et al.*, *Blood*, 1997, 89, 348703488 ("the Kwong article"), Saito, T., *et al.*, *Blood*, 1996, 87(2), 657-655 ("the Saito article") and Medline abstract number 82120536 ("the Douer abstract"). Applicants respectfully request reconsideration and withdrawal of the rejection because the presently claimed subject matter would not have been obvious in view of the cited art.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). And the proposed modification or combination of the prior art ***must have had a reasonable expectation of success***, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

"[W]hether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). "Obvious to try" situations arise where it might have been obvious to "explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). *See also Hybritech Inc. v. Monoclonal*

Antibodies, Inc., 802 F.ed. 1367, 1380 (Fed. Cir. 1986)("At *most*, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished.")(emphasis in original).

Preliminarily, claim 1 has been amended to recite methods for the treatment of acute myelomonocytic leukemia or acute erythroleukemia in a human, that comprise administering to the human a combination of a therapeutically effective amount of arsenic trioxide and all-trans retinoic acid. Support for the amendments is found throughout the specification as originally filed, including, for example, page 21, lines 7 to 9.

Upon review of the references cited in the official action, those skilled in the art would not have reasonably expected at the time of the invention that a combination of arsenic trioxide and all-trans retinoic acid could have been successfully used to treat acute myelomonocytic leukemia and acute erythroleukemia in humans. At most, the prior art might have provided persons skilled in the art with a suggestion *to try* to use a combination of arsenic trioxide and all-trans retinoic acid to treat these cancers, but much more is required to establish *prima facie* obviousness.

The Shen article describes treatment of 15 patients having relapsed acute promyelocytic leukemia (APL) with arsenic trioxide.[1] Two of the fifteen patients were also treated with low-dose all-trans retinoic acid.[2] Notably, the article only describes treatment of patients having APL, and does not describe or suggest treatment of cancers other than APL with a combination of arsenic trioxide and all-trans retinoic acid.

The Chen article describes the treatment of patients suffering from APL with arsenic trioxide.[3] The article does not teach or suggest treatment of APL with a combination of arsenic trioxide and all-trans retinoic acid, much less teach or suggest treatment of cancers other than APL with a combination of arsenic trioxide and all-trans retinoic acid.

The Kwong article describes studies in which patients having relapsed APL were treated with arsenic trioxide.[4] The article describes further studies in which patients having chronic myeloid leukemia (CML) were treated with arsenic trioxide.[5] Again, the article fails

[1] Page 3354, second column.
[2] *Id.*
[3] Page 3348, second column.
[4] Page 3487, first column.
[5] Page 3487, second column.

to teach or suggest treatment of patients suffering from APL, CML, or any type of cancer, with a combination of arsenic trioxide and all-trans retinoic acid, and, significantly, states that "[b]ecause of the considerable toxicities and the possible and still undefined long-term sequelae, the usefulness of As_2O_3 in the modern treatment of leukemia is still unclear...the biological and pharmacological actions of arsenic must be further investigated to define its role in the treatment of leukemia and other types of malignancies."[6]

The Saito article suggests that all-trans retinoic acid may have efficacy as a therapeutic agent against disseminated intravascular coagulation syndrome (DIC) that occurs in connection with APL and acute monoblastic leukemia, also known as acute monocytic leukemia.[7] The article fails to indicate, however, that all-trans retinoic acid may be effective against DIC that occurs in connection with cancers other than APL and acute monoblastic leukemia, and does not teach or suggest that As_2O_3 in combination with all-trans retinoic acid may be effective against DIC.

The Douer abstract indicates that all-trans retinoic acid inhibited the clonal growth of APL and acute myeloblastic leukemia cells *in vitro*. The abstract fails to teach or suggest, however, that ATRA would inhibit the growth of other types of leukemia cells, and fails to teach or suggest that ATRA in combination with As_2O_3 would be effective at inhibiting the growth of leukemia cells.

The references cited in the official action thus fail to teach or suggest that a combination of arsenic trioxide and all-trans retinoic acid could be successfully used to treat acute myelomonocytic leukemia or acute erythroleukemia in humans. Rather, the references indicate that arsenic trioxide and all-trans retinoic acid have been administered in combination to humans to treat APL, and indicate that arsenic trioxide administered alone has been used to treat patients suffering from APL and CML. The references further indicate that all-trans retinoic acid inhibited the growth of APL and acute myeloblastic leukemia cells *in vitro*, and suggest that all-trans retinoic acid may be effective as a therapeutic agent against DIC that occurs in connection with APL and acute monocytic leukemia. But the references do not indicate that a combination of arsenic trioxide and all-trans retinoic acid have

[6] Page 3488.
[7] Page 657, first column.

previously been used to treat patients suffering from acute myelocytic leukemias other than APL.

As understood by those skilled in the art at the time of the invention, there are many different types of acute and chronic myelocytic leukemias, and different approaches have been taken towards treating the different types of acute and chronic myelocytic leukemias. AML subtypes other than APL have typically been treated with cytarabine and an anthracycline (such as daunorubicin).[8] APL, however, has almost universally been treated with all-trans retinoic acid and induction chemotherapy.[9] Patients having non-APL AML's have thus typically received treatments that differ from those given to APL patients. Accordingly, those skilled in the art would have appreciated at the time of the invention that the efficacy of a particular anti-cancer agent or agents against APL was not predictive of its efficacy against other subtypes of AML due to the different approaches that have proven successful for treating APL and non-APL AML's.

Those skilled in the art would thus not have reasonably expected that a combination of arsenic trioxide and all-trans retinoic acid could have been successfully used to treat non-APL AML subtypes in humans just because the combination had been reported to have efficacy against APL. Although those skilled in the art might arguably have considered trying to use a combination of arsenic trioxide and all-trans retinoic acid to treat acute myelomonocytic leukemia and acute erythroleukemia, the results of doing so could not have been predicted with a reasonable degree of certainty. Accordingly, those skilled in the art at the time of the invention would not have reasonably expected that a combination of arsenic trioxide and all-trans retinoic acid could have been successfully used to treat acute myelomonocytic leukemia and acute erythroleukemia in humans. Applicants thus respectfully submit that the presently claimed subject matter would not have been obvious at the time of the invention, and accordingly, respectfully request withdrawal of the rejection.

B. Claims 1, 3 to 12, 19 to 22, and 24 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Shen article in view of the Chen article, the Kwong article, the Saito article, the Douer abstract, and U.S. patent number 4,599,305 ("the Witte

[8] Appelbaum, F.R., *et al.*, *Hematology*, 2001, 62-86 (attached as Exhibit B to the reply filed November 1, 2006). See page 65.
[9] *Id.* at 63.

patent"). Applicants respectfully request reconsideration and withdrawal of the rejection because the presently claimed subject matter would not have been obvious in view of the cited art.

As discussed above, upon review of the Shen, Chen, Kwong, and Saito articles and the Douer abstract, those skilled in the art would not have reasonably expected at the time of the invention that a combination of arsenic trioxide and all-trans retinoic acid could have been successfully used to treat acute myelomonocytic leukemia and acute erythroleukemia in humans, and the Witte patent does not cure the deficiencies of these references. The Witte patent teaches that different therapies are utilized for the treatment of different types of leukemias, and states that acute leukemia requires immediate treatment utilizing the full range of therapeutic measures available.[10] The patent, however, does not teach or suggest that the "full range of therapeutic measures" includes a combination of arsenic trioxide and all-trans retinoic acid. Moreover, the patent does not describe or suggest treatment of acute myelomonocytic leukemia and acute erythroleukemia with a combination of arsenic trioxide and all-trans retinoic acid.

Accordingly, for the reasons discussed above, those skilled in the art at the time of the invention would not have reasonably expected that a combination of arsenic trioxide and all-trans retinoic acid could have been successfully used to treat acute myelomonocytic leukemia and acute erythroleukemia in humans. The presently claimed subject matter would thus not have been obvious, and Applicants accordingly, respectfully request withdrawal of the rejection.

[10] Col. 1, lns. 39 to 45.

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Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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Christy Cheever
Attorney of Record
Registration No. 52,722

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355
Telephone: (610) 883-5743
Facsimile: (610) 727-7651